REMARKS

In the Office Action dated February 22, 2007, claims 1-14 are pending. The Examiner has made the Restriction Requirement final. Consequently, claims 5 and 8-14 have been withdrawn from further consideration as directed to non-elected subject matter. Claims 1-4 and 6-7, and SEQ ID NO: 4, are examined and are rejected. Specifically, claims 1-4 and 6-7 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over McIntosh et al. (U.S. Patent No. 6,767,896 B1). Claims 1-4 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly unpatentable over Claims 2, 5, 6, 12, 13, 15-21, 38-41, 43, 45, 47 and 49 of co-pending Application No. 10/537,088. Further, claims 5, 6 and 7 are objected to as dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 1-4 and 6-7 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over McIntosh et al. (U.S. Patent No. 6,767,896 B1) (hereinafter "McIntosh").

McIntosh claims a conotoxin peptide in claim 1, which is characterized by a general formula I, as set out in SEQ ID NO: 1:

$$Xaa\text{-}Xaa_0\text{-}Xaa_1\text{-}Cys\text{-}Cys\text{-}Gly\text{-}Xaa_2\text{-}Xaa_3\text{-}Xaa_4\text{-}Cys\text{-}Xaa_5\text{-}Xaa_6\text{-}Cys\text{-}Xaa_7.$$

Each of Xaa, Xaa_1, Xaa_2, Xaa_3, Xaa_4, Xaa_5, Xaa_6, and Xaa_7 (i.e., nine out of the fourteen amino acid positions) is characterized as selectable from a Markush group of possible amino acid residues.

The Examiner states that the possible choices for each amino acid position, recited in claim 1 of MaIntosh, include all of those amino acids in instant SEQ ID NO: 4. According to the

Examiner, it is obvious to select members of a known Markush group for use in or as specific embodiments or species of the genus described by the Markush group. The Examiner also contends that the selection of the second amino acid through to the penultimate amino acid (in SEQ ID NO: 4) is further compelled by the fact that these amino acids correspond to the natural product, χ-Mrl, A or AB, as disclosed in the instant specification as SEQ ID NOS: 1 and 2, respectively, on page 2, lines 4 and 5. The Examiner states that the penultimate residue, the modified 4-hydroxyproline, is itself a natural, post-translational modification, as disclosed at lines 7-9, page 2 of the specification.

Moreover, the Examiner alleges that the use of or substitution with pyro-glutamate at the N-terminal end of a conotoxin sequence is also discussed by Jones et al. in U.S. Patent Application Publication 2005/0271589 A1 ("Jones"). Jones indicates in paragraph [0014], page 2, that the N-terminal Glutamine can be substituted with pyro-Glutamate, designated (Z) in the one-letter sequence codes. The Examiner contends that the use of an N-terminal pyro-glutamate appears to provide an obvious advantage, as Jones describes conotoxin peptide sequences from more than one species of the genus *Conus* (*C. miles, tulipa, sulcata, purpurascens,* and *geographicus*), to which N-terminal pyro-glutamates are attached or substituted regardless of the differences these conotoxins have with respect to the remainder of the peptide sequences. Jones similarly describes these common substitutions of conotoxin amino acids in U.S. Patent Application Publications 2004/0176278 and 2003/0170222.

Applicants respectfully disagree.

In the first instance, the Examiner states that it is obvious to select members of a known Markush group (i.e., as disclosed by McIntosh) for use as specific species of the genus described by the Markush group. In this connection, Applicants observe that as recited in claim

1 of McIntosh, Xaa, Xaa_1, Xaa_2, and Xaa_6 of formula I can be selected from a Markush group of 4, 11, 10, and 3 specific amino acid residues, respectively. For Xaa_3, Xaa_4, Xaa_5, and Xaa_7, the Markush group for each of these positions names 13, 14, 14, and 18 specific amino acids respectively, and additionally names more generic amino acids, such as "any non-natural aromatic amino acid", "any non-natural basic amino acid", for example. Therefore, formula I of McIntosh encompasses essentially an indefinite number of alternative sequences for a conotoxin. Applicants respectfully submit that McIntosh also does not provide any suggestion, or any reason, for those skilled in the art to make the specific selections for each amino acid position, essentially out of an indefinite number of possible combinations, in order to arrive at instant SEQ ID NO: 4. One would have to choose Pyro-Glu for Xaa, Gly for Xaa_0, Val Xaa_1, Tyr for Xaa_2, Lys for Xaa_3, Leu for Xaa_4, His for Xaa_5, Hyp for Xaa_6, and Des-Xaa_7 for Xaa_7, in order to arrive at instant SEQ ID NO: 4. Therefore, contrary to the Examiner's contention, Applicants submit that it is not obvious to select members of a known Markush group for use as specific species of the genus, if the genus contains essentially an indefinite number of species.

The Examiner then states that the selection of the second amino acid through to the penultimate amino acid (in SEQ ID NO: 4) is compelled by the fact that these amino acids correspond to the natural product, χ-Mrl, A or AB. Applicants respectfully submit that there is no teaching in McIntosh that suggests that preferred selections are those that correspond to the amino acids in a natural conotoxin. In fact, in McIntosh, the only conotoxin peptides disclosed that have the second amino acid through to the penultimate amino acid selected to be precisely those of the natural conotoxin, are the natural conotoxin peptide itself (Mar1) and another conotoxin peptide allegedly also isolated from venom of *C. marmoreus* (Mar2, missing the N-terminal Asn as compared to Mar1). There is absolutely no teaching or suggestion anywhere in

McIntosh to substitute the N-terminal Asn of Mar1 with pyro-Glu, or add pyro-Glu to the N-terminus of Mar2.

The Examiner has apparently relied upon Jones to supply what is missing from McIntosh. Applicants submit that the Examiner should have then formally cited Jones in stating the rejection, i.e., it is a rejection under §103 based on a combination of McIntosh and Jones.

Applicants respectfully submit that although the broad generic peptide structures set out in the publications of Jones encompass peptides with an N-terminal pyroglutamate, it is clear that, when these Jones publications are read as a whole, an N-terminal pyroglutamate is only contemplated as a substitution for an N-terminal glutamine. In this regard, in the summary of then invention in each of the Jones publications appears the following statement:

"The N-terminal Gln may be substituted with pyro-glutamate (Z)."

The description is part of a long laundry list of potential substitutions of which there are an indefinite number. There is no evidence or indication in any of the Jones publications that any such substitution was actually made, or any was naturally occurring. Importantly, the only residue for which pyroglutamate was indicated as a potential substitution was an N-terminal Gln. This Gln to pyro-Glu substitution was most probably included by Jones, as it was known that N-terminal glutamine residues, under normal conditions, will cyclise to form Z (i.e., pyro-Glutamate). On the other hand, such a process does not occur in the case of N-terminal Asn residues. These residues just do not form Z residues and therefore, in contrast to the Examiner's assertion, Asn to Z is not a common or obvious substitution.

In contrast, the present invention is based on the recognition that a particular type of substitution (such as pyro-Glu) at the N-terminus of a chi-conotoxin peptide leads to surprisingly improved properties. See, for example, page 4, lines 8 to 19 and Table 3 on page 32. In

particular, chi-conotoxin peptides with an N-terminal pyro-Glu substitution of Asn, are found to be especially stable. MrIA (SEQ ID NO: 1) was found to be almost completely converted to degradation products after 31 days, whereas the instant conotoxin peptide of SEQ ID NO: 4 (with an N-terminal pyro-Glu substitution of Asn as compared to MrIA) remained more than 99% pure. Additionally, as described on page 4, lines 15-17, when tested in a rat neuropathic model, the conotoxin peptide of SEQ ID NO: 4 was found to have greater maximum efficacy relative to MrIA. These surprising properties make these N-substituted peptides superior drug candidates than the native peptides or other analogues, even those analogues having higher potency in *in vitro* assays. Therefore, Applicants respectfully submit that the superior properties of a conotoxin peptide with a N-terminal pyro-Glu substitution, would not have been expected or predicted by those skilled in the art, even in light of the disclosures of McIntosh and Jones.

Applicants further submit that an analysis of the obviousness is governed by the Supreme Court's recent decision in *KSR Int'l Co. v. Teleflex Inc.* (550 U.S. ___, 2007 WL 1237837 (2007)). The *KSR* Court held that the Teaching, Suggestion or Motivation (TSM) test shouldn't be applied rigidly. However, the Court acknowledged that the TSM test still provides a helpful insight to the obviousness question. *Id.*, at 15. In addition, with respect to a combination of patents, the Court indicated that an invention is not obvious if the combination of old elements is not a predictable use of these elements according to their established functions giving predictable results. See, e.g., *Id.*, at 13 (emphasis added). The *KSR* Court also highlighted the importance of secondary considerations and upheld the use of the "teaches away" argument to disprove obviousness. See, e.g., *Id.*, at 12.

In a MEMORANDUM issued by the Patent Office dated May 3, 2007, relating to the *KSR* decision, the Patent Office states that "in formulating a rejection under 35 U.S.C. § 103(a)

based upon a combination of prior art elements, it remains necessary to identify reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." (Emphasis added.)

In the present case, Applicants respectfully submit that there is no suggestion in either McIntosh or Jones that a replacement of Asn with pyro-Glu in a natural conotoxin peptide is feasible (to be chemically synthesized) or desirable. Those skilled in the art would not have had any motivation, or any "reason" (see the MEMORANDUM from the Patent Office, discussed above), to make such a substitution. Additionally, Applicants respectfully submit that the superior properties of the presently claimed conotoxin peptide with a N-terminal pyro-Glu substitution, including significantly improved stability and greater *in vivo* efficacy, would not have been predicted by those skilled in the art in light of the disclosures of McIntosh and Jones.

Accordingly, it is respectfully submitted that the presently claimed invention is not obvious in view of the cited references. The rejection of claims 1-4 and 6-7 under 35 U.S.C. §103(a) based on McIntosh is overcome, and withdrawal thereof is respectfully requested.

Claims 1-4 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over Claims 2, 5, 6, 12, 13, 15-21, 38-41, 43, 45, 47 and 49 of copending Application No. 10/537,088.

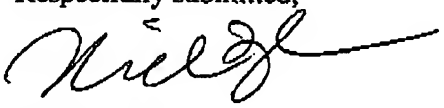
Applicants observe that this is a provisional rejection because the conflicting claims have not in fact been patented. Applicants also observe that no official action on the merits has issued in copending Application No. 10/537,088. Applicants intend to address this double patenting rejection at a later time.

Finally, the Examiner has stated that claims 5, 6 and 7 are objected to as dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

It is unclear to Applicants whether the Examiner would allow claim 5, drawn to SEQ ID NOS: 10 and 11, which has not been examined on the merits. Additionally, Applicants observe that claim 6 is included in the obviousness rejection based on McIntosh. Therefore, Applicants respectfully seek clarification from the Examiner with respect to claims 5-7.

In view of the foregoing remarks, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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